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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/840,146	04/24/2001	Harlan W. Waksal	11245/46604	5311

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EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1642	12

DATE MAILED: 11/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application N .	Applicant(s)	
	09/840,146	WAKSAL, HARLAN W.	
	Examin r	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE f this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-138* is/are pending in the application.

4a) Of the above claim(s) *48-50,59-72 and 77-125* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-47,51-58,73-76 and 126-138* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment and response to the restriction requirement, filed May6, 2003, is acknowledged. Applicant elected group I with traverse and elected the species of an EGFR antagonist that is an anti-EGFR antibody. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Applicant added new claims 128-138 (misnumbered in the amendment as 129-139). Correction of the numbering of the claims is required in response to this Office action. Claims 36-138 are pending.

3. Claims 36-47, 51-58, 73-76, 126 and 127 are examined on the merits. Claims 59-72 and 77-125 do not read on the elected species and are withdrawn from consideration, because the elected species reads on the prior art. In view of the amendment to claims 48-50, these claims do not read on the elected species, and are withdrawn from consideration.

Claim Rejections Withdrawn:

4. The rejection of claims 48-50 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn in view of the amendment.

5. The rejection of claims 36-47, and 51-53 under 35 U.S.C. 103(a) as being unpatentable over Baselga (J. Nat. Cancer Inst., 85: 1327-1333, 1993), Fan (Cancer Res., 53: 4637-4642, 1993) or Baselga (Breast Cancer Res. Treatment, 29: 127-138, 1994) in view of Mendelsohn (U.S. Patent 4,943,533; issued July, 1990) is withdrawn in view of the amendment to claim 36.

6. The rejection of claims 36, 54-58 and 126 under 35 U.S.C. 103(a) as being unpatentable over Prewett and further in view of either Mateo de Acosta del Rio (U.S. Patent 5,891,996; issued Apr. 6, 1999; filing date Nov. 17, 1995) or Bendig (U.S. Patent 5,558,864; issued Sep. 24, 1996; filed Nov. 6, 1992) is withdrawn in view of the amendment to claim 36.

7. The rejection of claims 36, 74 and 127 under 35 U.S.C. 103(a) as being unpatentable over Baselga (Breast Cancer Res. Treatment, 29: 127-138, 1994) in combination with Prewett and further in view of Punt (Punt, Cancer, 83: 679-689, 1998) is withdrawn in view of the amendment to claim 36.

New Grounds of Rejection:

8. Claims 36-38, 41, 43-47, 51-53, 58, 73, 74, 75 and 136-138 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schlessinger (U.S. Patent 6,217,866; issued April 17, 2001; effective filing Jun. 29, 1993) in view of Rockwell (Rockwell, P. et al. Molecular and Cellular Differentiation, 3(4): 315-335, 1995) and further in view of either Fischer-Colbrie (Fischer-Colbrie, J. et al., Anticancer Res. 17(1B): 613-619, 1997; Abstract only) or Turkeri (Turkeri, L.N., et al. Urology, 51(4): 645-649, 1998, Apr.; Abstract only).

The claimed inventions are drawn to methods for inhibiting the growth of a refractory tumor comprising administering an epidermal growth factor receptor (EGFR) antagonist that is an anti-EGFR antibody, and a chemotherapeutic agent to a human having a refractory tumor that has failed or been resistant to treatment with an antineoplastic, wherein administration is effective to inhibit growth of the refractory tumor. The tumor may overexpress EGFR, the tumor may be any of a breast, heart, lung, small intestine, colon, spleen, kidney, bladder, head and neck, ovary, prostate, brain, pancreas, skin, bone, bone marrow, blood, thymus, uterus, testicles, cervix, or liver. The anti-EGFR antibody may be administered intravenously, or may be administered prior to administration of the chemotherapeutic agent. The dose of the antibody may be about 10 to about 500 mg/m^2 weekly. The anti-EGFR antibody may inhibit stimulation of EGFR by its ligand, may inhibit binding of EGFR to its ligand, or may bind EGFR externally. The anti-EGFR antibody may inhibit EGFR phosphorylation, or inhibit tyrosine kinase activity. The dose of the antibody may be sufficient to saturate EGFR. The chemotherapeutic agent may be any one of those listed in claims 73, or may be cisplatin, doxorubicin, paclitaxel, Irinotecan(CPT-11), or topotecan or a combination thereof.

Schlessinger teaches methods of inhibiting the growth of human tumor cells that express human EGF receptors comprising administering an anti-neoplastic agent and a monoclonal antibody to a human cancer patient (see claim 1). Schlessinger teaches administration of antibody with doxorubicin and also with cisplatin. (col. 17, line 50 – col. 18, line 3). Schlessinger teaches that this method is useful to solve problems arising in the clinic, such as the development of resistance to drugs and toxicity of antineoplastic, because of a synergistic effect of the combination of an anti-EGFR antibody and anti-neoplastic agents (col. 8, line 45 – col. 9,

line 12). Schessinger teaches monoclonal antibodies that inhibit binding of EGF to EGFR (col. 15, lines 22-28). Such antibodies would therefore, be antibodies that inhibited stimulation of EGFR by EGF, would bind to EGFR externally, would inhibit EGFR phosphorylation and inhibit tyrosine kinase activity, because binding of EGF to EGFR occurs extracellularly and causes stimulation of EGFR, phosphorylation and tyrosine kinase activity of EGFR. Schlessinger fails to explicitly teach methods where the human has a refractory tumor that has failed or been resistant to treatment with an antineoplastic.

Rockwell teaches that a rationale for the augmentation by an anti-EGFR agent (such as an anti-EGFR antibody) of the effects of a DNA-damaging drug, is that an anti-EGFR antibody blocks activation of the EGFR, and thereby blocks recovery of cells surviving the initial chemotherapeutic insult (pages 318-319).

Turkeri teaches that expression of EGF and TGF-alpha (ligands that stimulate EGFR) is correlated with tumor recurrence in bladder cancer patients (see abstract).

Fischer-Colbrie teaches EGFR status correlates with an impaired response to chemotherapy containing platinum compounds in ovarian cancer patients (see abstract).

The claimed inventions are obvious over the prior art, because although Schlessinger fails to explicitly teach treatment of patients having a refractory tumor, the motivation to treat such a population of patients is provided by the prior art. Rockwell teaches that growth factors that stimulate EGFR appear to play a role in resistance of cancer cells to anti-neoplastic treatment. This is substantiated by the teachings of Turkeri that levels of EGFR ligands are correlated with recurrance of bladder cancer, and by the teachings of Fischer-Colbrie that EGFR status correlates with an impaired response to chemotherapy in ovarian cancer patients. Thus, it would have been

prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the method of Schlessinger to treat patients having a refractory tumor. One would have had a reasonable expectation of success because of the known role of EGFR signaling in chemoresistance and poor prognosis of cancers.

The claimed methods are also drawn to methods comprising the administration of specific dosages of EGFR antagonist.

Methods for determining specific dosages and dosing schedules are within the skill of one having ordinary skill in the art and would have been obvious to one of ordinary skill in the art at the time the invention was made.

9. Claims 36, and 53-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schlessinger (U.S. Patent 6,217,866; issued April 17, 2001; effective filing Jun. 29, 1993) in view of Rockwell (Rockwell, P. et al. Molecular and Cellular Differentiation, 3(4): 315-335, 1995) and further in view of either Fischer-Colbrie (Fischer-Colbrie, J. et al., Anticancer Res. 17(1B): 613-619, 1997) or Turkeri (Turkeri, L.N., et al. Urology, 51(4): 645-649, 1998, Apr.); and further in view of Mateo de Acosta del Rio (U.S. Patent 5,891,996; issued Apr. 6, 1999; filing date Nov. 17, 1995; cited in a previous Office action) or Bendig (U.S. Patent 5,558,864; issued Sep. 24, 1996; filed Nov. 6, 1992; cited in a previous Office action).

The claimed inventions read on methods comprising the administration of antibodies that are chimeric, comprising a human constant region, humanized or human.

The combination of Schlessinger, Rockwell, and Fischer-Colbrie, or Turkeri fails to teach chimeric, human or humanized antibodies to EGFR. However, either of Mateo de Acosta del

Rio or Bendig teaches methods for making such antibodies and the benefits of altering non-human antibodies to comprise human. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have altered the invention of Schlessinger so that the antibodies of Schlessinger were chimeric, human or humanized.

10. Claims 36, 39, 40, 126, and 128-134 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schlessinger (U.S. Patent 6,217,866; issued April 17, 2001; effective filing Jun. 29, 1993) in view of Rockwell (Rockwell, P. et al. Molecular and Cellular Differentiation, 3(4): 315-335, 1995) and further in view of either Fischer-Colbrie (Fischer-Colbrie, J. et al., Anticancer Res. 17(1B): 613-619, 1997) or Turkeri (Turkeri, L.N., et al. Urology, 51(4): 645-649, 1998, Apr.); and further in view of Modjtahedi (Modjtahedi, H. et al. British J. Cancer, 73: 228-235, 1996).

The claimed inventions read on methods comprising treatment of humans having head and neck squamous cell refractory tumors. While the combination of Schlessinger, Rockwell and either Fischer-Colbrie or Turkeri generally teaches the treatment of refractory tumors, the combination fails to teach methods for treatment of refractory head and neck squamous cell tumors. However, it is known in the art that head and neck squamous tumors express EGFR as evidenced by the teachings of Modjtahedi. Modjtahedi teaches that EGFR is overexpressed in bladder, brain, head and neck, pancreas, lung, breast and ovarian cancers (see page 228, 1st col.). Modjtahedi also teaches a method comprising the administration of an anti-EGFR antibody to patients with head and neck cancer or lung cancer, where the patients were ones that had received prior treatment (assumed to be resistant because the patients were enrolled in the trial

and had a confirmed diagnosis of squamous cell carcinoma of the lung or head and neck, see page 229, 2nd col). Modjtahedi also contemplates methods of treatment using a chimeric or humanized antibody (page 234, 1st to 2nd col., bridging sentence). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the method of Schlessinger in the treatment of refractory head and neck tumors.

The claimed inventions are also directed to methods comprising specific loading doses and weekly doses. Methods for determining specific dosages and dosing schedules are within the skill of one having ordinary skill in the art and would have been obvious to one of ordinary skill in the art at the time the invention was made.

11. Claims 36, 39, 127, 134 and 135 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schlessinger (U.S. Patent 6,217,866; issued April 17, 2001; effective filing Jun. 29, 1993) in view of Rockwell (Rockwell, P. et al. Molecular and Cellular Differentiation, 3(4): 315-335, 1995) and further in view of either Fischer-Colbrie (Fischer-Colbrie, J. et al., Anticancer Res. 17(1B): 613-619, 1997) or Turkeri (Turkeri, L.N., et al. Urology, 51(4): 645-649, 1998, Apr.); and further in view of or Messa (Messa, C. et al. Acta Oncologica, 37(3): 285-289, 1998) and further in view of Punt (Punt, Cancer, 83: 679-689, 1998; cited in a previous Office action).

The claimed inventions read on methods comprising treatment of humans having refractory colon tumors; and also reads on methods where irinotecan is the chemotherapeutic agent. While the combination of Schlessinger, Rockwell and either Fischer-Colbrie or Turkeri generally teaches the treatment of refractory tumors, the combination fails to teach methods for treatment

of refractory colon tumors; and also fails to specifically teach the use of irinotecan as the chemotherapeutic agent. However, it is known in the art that colon tumors express EGFR as evidenced by the teachings of Messa. Messa teaches that EGFR is expressed in human colorectal adenocarcinoma samples (see Table 1, page 286). Punt teaches that irinotecan is a new chemotherapeutic agent that is useful in the treatment of colorectal cancer. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have developed a method of treatment using anti-EGFR antibodies or chimeric anti-EGFR antibodies in combination with irinotecan for the treatment of colorectal cancer.

The claimed inventions are also directed to methods comprising specific loading doses and weekly doses. Methods for determining specific dosages and dosing schedules are within the skill of one having ordinary skill in the art and would have been obvious to one of ordinary skill in the art at the time the invention was made.

12. Claims 42 and 76 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that the specification lacks descriptive support for the claimed inventions.

In the case of claim 42, the invention comprises a method for inhibiting the growth of a refractory tumor comprising administering an EGFR antagonist that is an anti-EGFR antibody, wherein the administration is oral. Neither the originally filed claims nor the specification

describe a formulation comprising an anti-EGFR antibody that may be administered orally. The specification provides a general contemplation of administering chemotherapeutic agents either parenterally or enterally, but this is insufficient support for a method comprising the oral administration of an anti-EGFR antibody. Therefore, it does not appear that applicant was in possession of the claimed invention at the time of filing.

In the case of claim 76, the invention comprises a method for inhibiting the growth of a refractory tumor comprising administering an EGFR antagonist that is an anti-EGFR antibody in combination with a chemotherapeutic agent, and further in combination with an adjuvant. The originally filed claims do not support the claimed invention. The specification generally provides support for the addition of an adjuvant in the case of a method where an EGFR antagonist is administered alone, but there is no contemplation or description of methods comprising administering an anti-EGFR antibody together with a chemotherapeutic agent and an adjuvant. Therefore, it does not appear that applicant was in possession of the claimed invention at the time of filing.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Anne L. Holleran
Patent Examiner
November 17, 2003

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